CASTLE BIOSCIENCES

DecisionDx MELANOMA

Predicts individual risk of melanoma recurrence or metastasis including the likelihood of sentinel lymph node positivity

CastleTestInfo.com

DecisionDx MELANOMA

Table of Contents

In early stage melanoma, staging alone can miss patients with aggressive tumor biology.

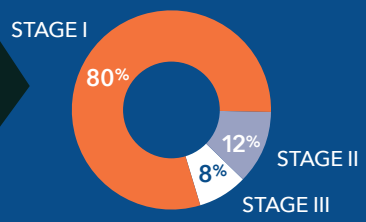
DecisionDx-MELANOMA

DecisionDx®-Melanoma more accurately predicts individual risk of recurrence including likelihood of sentinel lymph node positivity and informs clinical decision making.

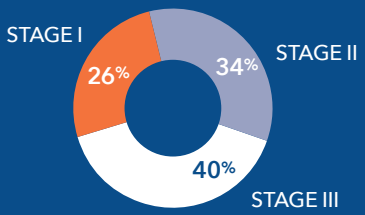
CASTLE BIOSCIENCES

AJCC staging-only approach misses patients with aggressive tumor biology

STAGE AT DIAGNOSIS*



MELANOMA DEATHS BY STAGE AT DIAGNOSIS*

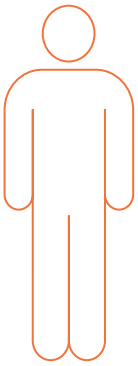


*Excludes stage IV

- Early detection of disease and lower tumor burden are associated with better patient response to therapy and survival outcomes.[1-5]
- Therefore, appropriate surveillance including imaging of high-risk patients is critical.[1-5]
- AJCC clinicopathologic factors are helpful clinically but can miss patients with aggressive tumor biology. The majority of deaths occur in patients diagnosed with early stage disease when using only these factors for staging.[6-8]
- Prognostic accuracy needs to be improved to determine the most appropriate melanoma management strategy for each patient.

DecisionDx-Melanoma Informs Two Important Clinical Decisions Impacting Treatment Plans[1-5]

Patient with **Stage I-III Melanoma**



DecisionDx-MELANOMA

- Quantifies expression of 31 genes from primary tumor using RT-PCR
- Applies a validated algorithm
- More accurately predicts the individual risk of recurrence or metastasis

Class 1A
Lowest Risk of recurrence and/or metastasis within 5 years

Class 1B/2A
Increased Risk of recurrence and/or metastasis within 5 years

Class 2B
Highest Risk of recurrence and/or metastasis within 5 years

RISK IDENTIFIED

CastleTestInfo.com

Case Profile: 52-year-old male with melanoma on the right lower leg

Breslow depth: 1.2 mm

Clark level not reported

No ulceration (T2a)

Mitotic rate: <1/mm^2

SLNB-eligible per NCCN: Yes

AJCC Clinical Stage: Stage IB (T2a)

Performed wide excision with sentinel lymph node biopsy per NCCN recommendation

- SLNB Negative
- Based on NCCN Guidelines for Stage IA/IB Patients with negative SLNB:
  - Low frequency clinical follow-up every 6-12 months (primarily with dermatology)
  - No advanced imaging or blood tests recommended
- Ordered DecisionDx-Melanoma for additional information

DecisionDx-Melanoma Test Result: Class 2B (HIGHEST RISK)

Updated Plan:

- **Patient sent to medical oncology for high intensity surveillance and clinical trial consideration**
- **Initial PET/CT scan - intense, abnormal uptake on the left lateral deep cervical node**
- **Biopsy and removal of left lateral deep cervical nodes**
- **Upgraded to stage IV due to metastatic disease in contralateral nodes**
- **Offered immunotherapy for low-burden metastatic disease**

Molecular Signature Result		Recurrence-Free Survival at 5 years (Stage I and II)	Distant Metastasis-Free Survival (Stage I and II)	Melanoma-Specific Survival (Stage I and II)
Class 1	1A 1B	95% 88%	97% 90%	99% 97%
Class 2	2A **2B**	77% **51%**	84% **65%**	97% **89%**

Stage I and II[9-12]
Approximately 67% of patients in the clinical validation studies were clinically and/or pathologically node-negative (AJCC Stage I and II). The test is an independent predictor of risk of recurrence compared to traditional clinicopathologic factors.

DecisionDx-MELANOMA

Informs 2 Key Clinical Management Decisions[9-22]

- Intensity of follow up, surveillance imaging and referral to surgical or medical oncology
- Sentinel Lymph Node Biopsy (SLNB) patient selection

Extensively Supported

- Over 30 peer-reviewed published studies including 2 meta-analyses[23-24]
- Achieves Level 1A evidence classification
- 230+ clinical US sites in collaboration with Castle Biosciences

Easily Integrates into Your Practice

- Online ordering available
- Results typically received within 3-5 days from sample receipt
- Favorable reimbursement profile — now covered by Medicare and multiple private insurers

References:

1. Poklepovic A et. al. *Oncology* 2018.
2. Ribas A et al. *JAMA* 2016.
3. Schadendorf D et al. *Eur J Can* 2017.
4. Robert C et al. *J Clin Oncol* 2017.
5. Joseph R et al. *Clin Cancer Res* 2018.
6. SEER data release 2017.
7. Whiteman D et al. *J Invest Dermatol* 2015.
8. Shaikh W et al. *J Natl Cancer Inst* 2016.
9. Gerami P et al. *Clin Cancer Res* 2015.
10. Gerami P et al. *J Am Acad Dematol* 2015.
11. Zager J et al. *BMC Cancer* 2018.
12. Gastman B et al. *J Am Acad Dermatol* 2019.
13. Vetto J et al. *Future Oncology* 2019.
14. Berger A et al. *CMRO* 2016.
15. Dillon L et al. *SKIN J Cutan Med* 2018.
16. Farberg A et al. *J Drugs Derm* 2017.
17. Schuitevoerder D et al. *J Drugs Derm* 2018.
18. Hyams D et al. *Future Oncology* 2020.
19. Scott A et al. *Am Surgeon* 2020.
20. Hsueh E et al. *JCO Precis Oncol* 2021.
21. Marsen et al. *SKIN J Cutan Med* 2021.
22. Arnot S et al. *Am J Surg* 2021.
23. Greenhaw B et al. *J Am Acad Dermatol* 2020.
24. Litchman G et al. *SKIN J Cutan Med* 2020.

CASTLE BIOSCIENCES

Contact us at:
866-788-9007
CastleBiosciences.com

Laboratory Address:
3737 N. 7th Street, Ste. 160
Phoenix, AZ 85014

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

Expert Panel: Clinical Workflow for DecisionDx®-Melanoma

DecisionDx MELANOMA

CLINICAL SUMMARY

A Dermatologist's Guide to Implementation of Gene Expression Profiling in the Management of Melanoma

Shawn G. Kwatra, MD; Howard Hines, MD; Yevgeniy R. Semenov, MD; Shannon C. Trotter, DO; Elizabeth Holland, RN, BSN; and Sancy Leachman, MD, PhD

OBJECTIVE

To provide clarification of use options and a rational clinical workflow to guide appropriate application of the 31-GEP test in everyday practice

DESIGN

Expert panel of five leading dermatologists with experience using the 31-GEP convened virtually in May 2020 and reviewed the following:

- ✓ Validation and clinical impact data supporting the use of sentinel lymph node biopsy
- ✓ Existing primary and meta-analyses for 31-GEP testing in melanoma risk assessment
- ✓ AJCC, NCCN, and Melanoma Prevention Working Group (MPWG) data and guidelines for GEP in melanoma risk assessment
- ✓ Experiences, rationales, and scenarios in which 31-GEP testing may be helpful for risk assessment

CONCLUSION

- The 31-GEP test is useful and actionable for patient care when applied in accordance with current NCCN guidelines
- The 31-GEP test can inform multidisciplinary conference discussion and can assist with determining the intensity of imaging, surveillance, and follow-up care
- Patient-specific features of the disease and individual circumstances should be considered in the decision to use 31-GEP testing
- It is important to incorporate a shared decision-making model implemented by the multidisciplinary team and the patient that is tailored to individual needs and preferences

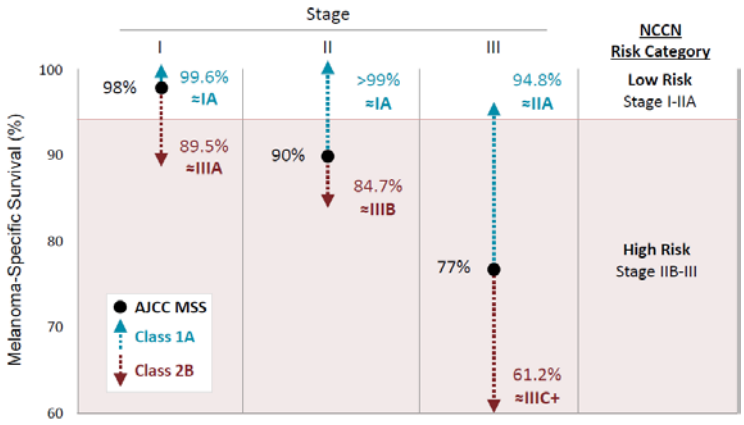


Figure 1. Data from cohort study (N=690) demonstrated that the 31-GEP test further informs risk analysis obtained by the American Joint Committee on Cancer (AJCC) staging protocol in patients with melanoma

METRICS	GEP % (95% CI)	SLNB % (95% CI)	GEP & SNLB % (95% CI)
RFS	**n=1,479**	**n=867**	**n=867**
Sensitivity	76 (71-80)	57 (51-63)	88 (84-92)
Specificity	76 (73-78)	74 (70-77)	52 (48-56)
DMFS	**n=1,223**	**n=867**	**n=867**
Sensitivity	76 (70-82)	61 (55-68)	90 (85-94)
Specificity	69 (66-72)	72 (68-75)	48 (44-52)

Table 1. Independent and combined accuracy metrics of GEP and SLNB in patients with GEP results and SLNB status

CI: Confidence interval; DMFS: distant metastasis-free survival; GEP: gene expression profile; RFS: recurrence-free survival; SLNB: sentinel lymph node biopsy

Adapted from Greenhaw et al. *J Am Acad Dermatol* 2020;83:745-53

BOTTOM LINE

The 31-GEP is supported by a robust and consistent body of evidence demonstrating clinical value in conjunction with SLNB for the prognosis of patients with melanoma. The panel recommends a clinical workflow that integrates 31-GEP testing under the umbrella of current national guidelines.

CASTLE BIOSCIENCES

Contact us at:
866-788-9007
www.CastleTestInfo.com

Laboratory Address:
3737 N. 7th Street, Ste. 160
Phoenix, AZ 85014

DDXCM-008v1-022021

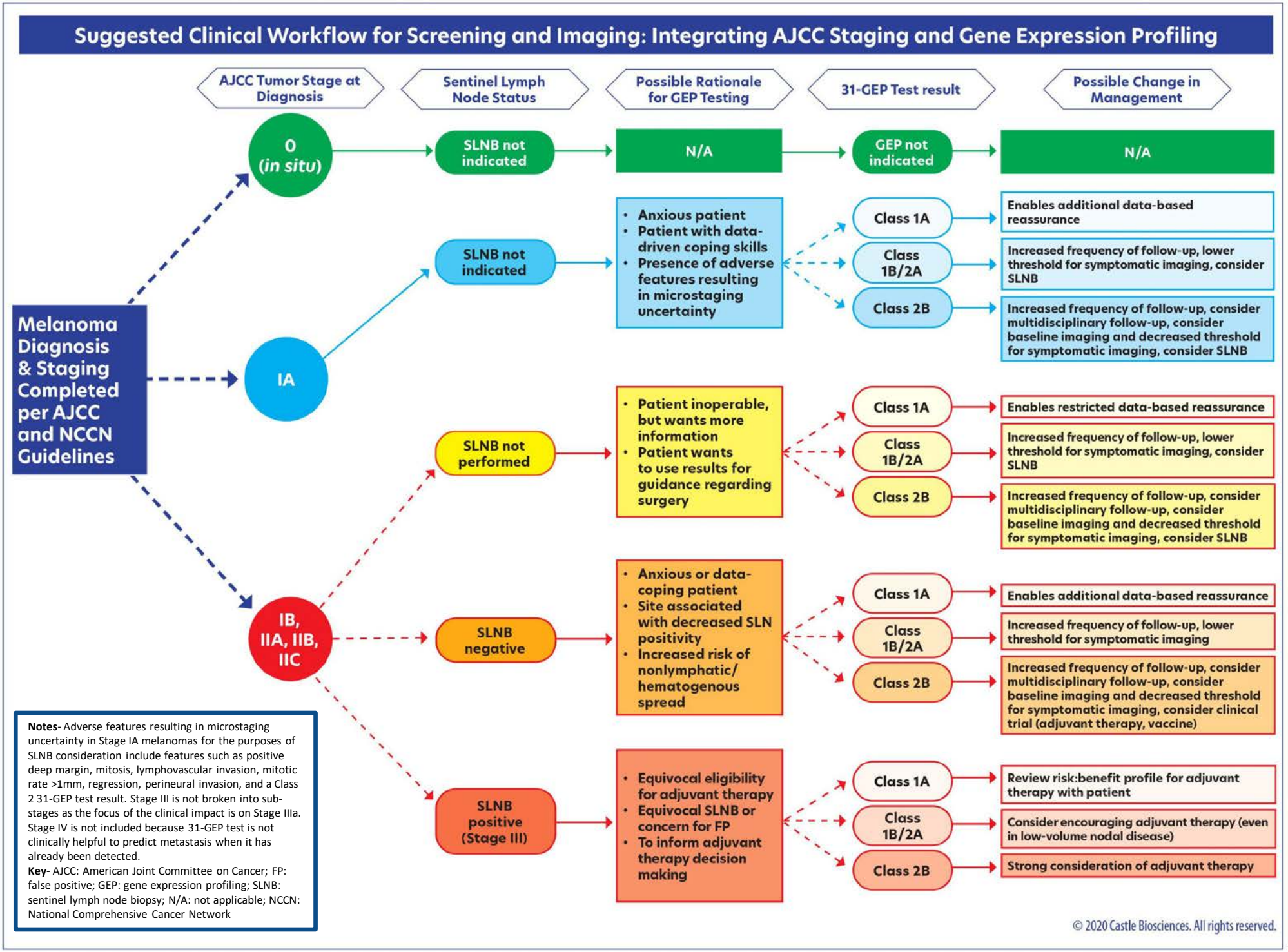


Figure 2. A proposed clinical algorithm for implementing 31-GEP testing in different clinical situations within current AJCC staging and integrating it into the NCCN guidelines for cutaneous melanoma

Integrated Test Report for Precise SLNB Positivity Risk

DecisionDx MELANOMA

CLINICAL SUMMARY

Integrating 31-Gene Expression Profiling With Clinicopathologic Features to Optimize Cutaneous Melanoma Sentinel Lymph Node Metastasis Prediction

Eric D. Whitman, MD; Vadim P. Koshenkov, MD; Brian R. Gastman, MD; Deri Lewis, MD; Eddy Hsueh, MD, et al. *JCO Precision Oncology* 2021; https://doi.org/10.1200/PO.21.00162

BACKGROUND

National guidelines recommend that the sentinel lymph node biopsy (SLNB) procedure can be considered for patients (T1-T4) with an expected risk of being SLN positive above 5% based on Breslow thickness and ulceration status. Use of this 5% threshold was based upon the 5% false negative rate for nodal recurrence as reported in one study, MSLT-I.[1] In addition, any patient above a 10% threshold should strongly consider having a SLNB. However, the overall rate of SLN positivity in the melanoma population is 12%, meaning that of those that undergo the SLNB procedure, 88% are negative.[2,3] In addition to the guideline recommendations, understanding the tumor biology can help better identify patients who would and would not benefit from the procedure.

OBJECTIVE

To determine if integration of the 31-gene expression profile (31-GEP) score combined with clinicopathologic factors in an artificial intelligence (AI)-trained algorithm accurately predicts sentinel lymph node (SLN) positivity for improved patient care

METHOD

An integrated 31-GEP (i31-SLNB) neural network algorithm incorporating clinicopathologic features with the continuous 31-GEP score was developed using a previously reported patient cohort (n = 1,398) and validated using an independent cohort (n = 1,674)

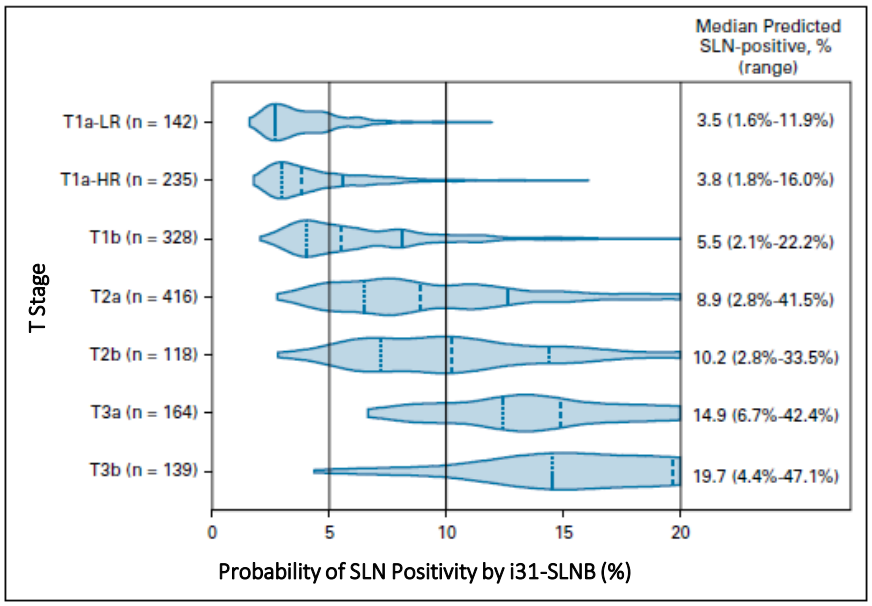


FIG 1. Distribution of SLN positivity risk predicted by i31-SLNB by T stage. T1a-LR refers to patients with T1a tumors with no high-risk features documented. T1a-HR refers to those with a T1a tumor who had risk factors for a positive SLN, including positive deep margins, mitotic index ≥2/mm^2 or lymphovascular invasion, considered to have a risk between 5% and 10%. The predicted risk was truncated at 20%. T4a risk ranged from 9.5% to 50.0%, and T4b ranged from 9.5% to 58.5%.

RESULTS

The i31-SLNB can improve personalized risk estimates for SLN positivity for better selection of those at high risk for a positive SLNB who may benefit most, and those who can safely forgo the procedure. Of all the factors, the 31-GEP score was the most predictive of a positive sentinel lymph node.

[1] Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med* 2014;370:599-609.
[2] Bamboat ZM, Konstantinidis IT, Kuk D, et al. Observation after a positive sentinel lymph node biopsy in patients with melanoma. *Ann Surg Oncol* 2014;21:3117-23.
[3] Ellis MC, Weerasinghe R, Corless CL, et al. Sentinel lymph node staging of cutaneous melanoma: predictors and outcomes. *Am J Surg* 2010;199:663-8.

Integrated Test Report for Precise SLNB Positivity Risk

DecisionDx MELANOMA

CLINICAL SUMMARY

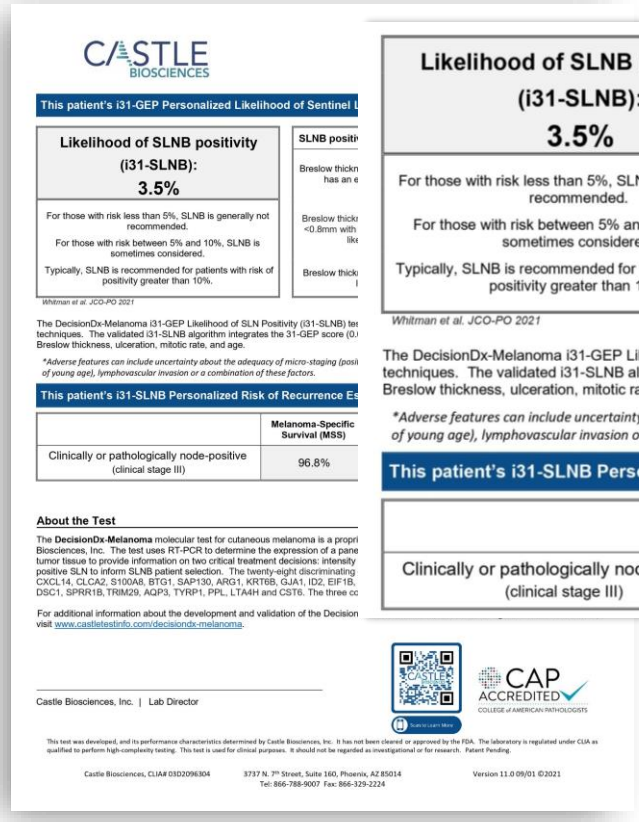
Precise and Personalized i31-SLNB for Sentinel Lymph Node Positivity

- Within the training and validation populations the SLNB-assessed positive rate is aligned with overall published positivity rates of 12%

- *Included in the i31-SLNB algorithm:
  - 31-GEP continuous score (ranging from 0-1)
  - Breslow thickness: mm
  - Ulceration: present or absent
  - Mitotic rate: /mm^2
  - Age: years

Of the variables included in the model, 31-GEP was the strongest predictor of SLN positivity

*Other variables evaluated for inclusion in this algorithm but not selected due to no additional risk prediction include: sex, regression, microstaging (positive deep margins), histological subtype, TILS, LVI, and tumor location



CASTLE BIOSCIENCES

This patient's i31-GEP Personalized Likelihood of Sentinel L

Likelihood of SLNB positivity (i31-SLNB): 3.5%

For those with risk less than 5%, SLNB is generally not recommended.

For those with risk between 5% and 10%, SLNB is sometimes considered.

Typically, SLNB is recommended for patients with risk of positivity greater than 10%.

Whitman et al. JCO-PO 2021

The DecisionDx-Melanoma i31-GEP Likelihood of SLN Positivity (i31-SLNB) te techniques. The validated i31-SLNB algorithm integrates the 31-GEP score (0. Breslow thickness, ulceration, mitotic rate, and age.

*Adverse features can include uncertainty about the adequacy of micro-staging (posi of young age), lymphovascular invasion or a combination of these factors.

This patient's i31-SLNB Personalized Risk of Recurrence Es

	Melanoma-Specific Survival (MSS)
Clinically or pathologically node-positive (clinical stage III)	96.8%

About the Test

The DecisionDx-Melanoma molecular test for cutaneous melanoma is a propri Biosciences, Inc. The test uses RT-PCR to determine the expression of a pane tumor tissue to provide information on two critical treatment decisions: intensity positive SLN to inform SLNB patient selection. The twenty-eight discriminating CXCL14, CLCA2, S100A8, BTG1, SAP130, ARG1, KRT6B, GJA1, ID2, EIF1B, DSC1, SPRR1B, TRIM29, AQP3, TYRP1, PPL, LTA4H and CST6. The three co

For additional information about the development and validation of the Decision visit www.castletestinfo.com/decisiondx-melanoma.

Castle Biosciences, Inc. | Lab Director

CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS

This test was developed, and its performance characteristics determined by Castle Biosciences, Inc. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Patent Pending.

Castle Biosciences, CLIA# 03D2096304 | 3737 N. 7th Street, Suite 160, Phoenix, AZ 85014 Tel: 866-788-9007 Fax: 866-329-2224 | Version 11.0 09/01 ©2021

Likelihood of SLNB positivity (i31-SLNB): 3.5%

For those with risk less than 5%, SLNB is generally not recommended.

For those with risk between 5% and 10%, SLNB is sometimes considered.

Typically, SLNB is recommended for patients with risk of positivity greater than 10%.

Whitman et al. JCO-PO 2021

SLNB positivity estimates using histopathologic factors alone:

Breslow thickness of <0.8mm without ulceration or other adverse features* has an estimated likelihood of SLNB positivity of **less than 5%**

Breslow thickness of ≥0.8 – 1.0mm with or without ulceration or thickness <0.8mm with ulceration and/or other adverse features* has an estimated likelihood of SLNB positivity **between 5% and 10%**

Breslow thickness of >1.0mm with or without ulceration has an estimated likelihood of SLNB positivity **greater than 10%**

The DecisionDx-Melanoma i31-GEP Likelihood of SLN Positivity (i31-SLNB) test result was developed using artificial intelligence techniques. The validated i31-SLNB algorithm integrates the 31-GEP score (0.0 – 1.0) with the patient's specific clinicopathologic factors of Breslow thickness, ulceration, mitotic rate, and age.

Adverse features can include uncertainty about the adequacy of micro-staging (positive deep margin), mitotic index ≥2/mm^2 (particularly in the setting of young age), lymphovascular invasion or a combination of these factors.

This patient's i31-SLNB Personalized Risk of Recurrence Estimates (5-year, AJCC Stage III):

	Melanoma-Specific Survival (MSS)	Distant Metastasis-Free Survival (DMFS)	Recurrence-Free Survival (RFS)
Clinically or pathologically node-positive (clinical stage III)	96.8%	86.4%	82.2%

View Full Publication

BOTTOM LINE

- i31-SLNB can provide a precise and personalized likelihood of sentinel lymph node positivity for patient management and guidance on sentinel lymph node biopsy

CASTLE BIOSCIENCES

Contact us at:
866-788-9007
www.CastleTestInfo.com

Laboratory Address:
3737 N. 7th Street, Ste. 160
Phoenix, AZ 85014

DDXCM-021v1-112021

NEW INTEGRATED TEST RESULT WITH PRECISE AND PERSONALIZED i31-ROR AND i31-SLNB

DecisionDx-MELANOMA HCP Guide to the Patient Report

Personalized Risk Prediction Integrated with Clinicopathologic Factors

NEW provides individual patient **clinicopathologic factors** used for integrated test result algorithms.

DecisionDx-Melanoma Class Result

Class 1A	**Lowest risk** of recurrence and/or metastasis within 5 years (GEP score 0 to 0.41)
Class 1B/2A	**Increased risk** of recurrence and/or metastasis within 5 years (GEP score >0.41 to <0.59)
Class 2B	**Highest risk** of recurrence and/or metastasis within 5 years (GEP score 0.59 to 1.0)

SLNB positivity information on page 2

5-Year Outcomes for Stage I or II Patients

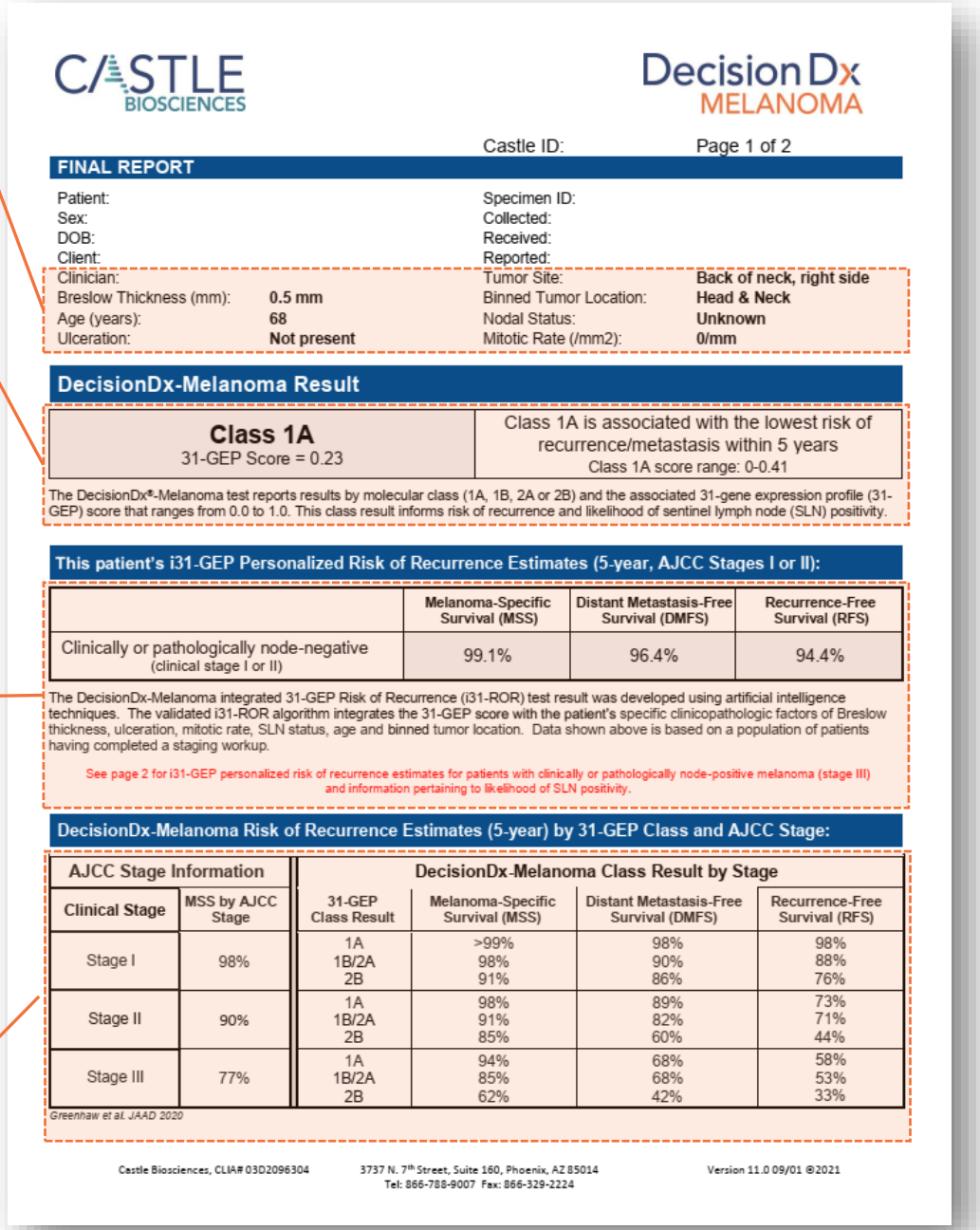
NEW i31-ROR Personalized Risk of Recurrence Estimates

Personalized 5-year outcomes for melanoma specific survival (MSS), distant metastasis-free survival (DMFS) and recurrence-free survival (RFS).

- A validated algorithm combines the 31-GEP score with clinicopathologic factors: Breslow thickness, age, ulceration, binned tumor location, nodal status and mitotic rate.
- *i31-ROR Personalized Risk Estimates for Stage III patients are provided on page 2*

MSS, DMFS and RFS risk prediction by DecisionDx-Melanoma class result provided for AJCC clinical stages I-III

- DecisionDx-Melanoma class **refines risk estimates** for survival when compared to AJCC v8.
- **Significant difference** between lowest risk (Class 1A) and highest risk (Class 2B) for all stages and all outcomes.
- For reference, the table now includes 5-year MSS by AJCC stage.



CASTLE BIOSCIENCES — DecisionDx MELANOMA

Castle ID: Page 1 of 2

FINAL REPORT

Patient:		Specimen ID:	
Sex:		Collected:	
DOB:		Received:	
Client:		Reported:	
Clinician:		Tumor Site:	Back of neck, right side
Breslow Thickness (mm):	0.5 mm	Binned Tumor Location:	Head & Neck
Age (years):	68	Nodal Status:	Unknown
Ulceration:	Not present	Mitotic Rate (/mm2):	0/mm

DecisionDx-Melanoma Result

Class 1A 31-GEP Score = 0.23	Class 1A is associated with the lowest risk of recurrence/metastasis within 5 years Class 1A score range: 0-0.41

The DecisionDx®-Melanoma test reports results by molecular class (1A, 1B, 2A or 2B) and the associated 31-gene expression profile (31-GEP) score that ranges from 0.0 to 1.0. This class result informs risk of recurrence and likelihood of sentinel lymph node (SLN) positivity.

This patient's i31-GEP Personalized Risk of Recurrence Estimates (5-year, AJCC Stages I or II):

	Melanoma-Specific Survival (MSS)	Distant Metastasis-Free Survival (DMFS)	Recurrence-Free Survival (RFS)
Clinically or pathologically node-negative (clinical stage I or II)	99.1%	96.4%	94.4%

The DecisionDx-Melanoma integrated 31-GEP Risk of Recurrence (i31-ROR) test result was developed using artificial intelligence techniques. The validated i31-ROR algorithm integrates the 31-GEP score with the patient's specific clinicopathologic factors of Breslow thickness, ulceration, mitotic rate, SLN status, age and binned tumor location. Data shown above is based on a population of patients having completed a staging workup.

See page 2 for i31-GEP personalized risk of recurrence estimates for patients with clinically or pathologically node-positive melanoma (stage III) and information pertaining to likelihood of SLN positivity.

DecisionDx-Melanoma Risk of Recurrence Estimates (5-year) by 31-GEP Class and AJCC Stage:

AJCC Stage Information		DecisionDx-Melanoma Class Result by Stage			
Clinical Stage	MSS by AJCC Stage	31-GEP Class Result	Melanoma-Specific Survival (MSS)	Distant Metastasis-Free Survival (DMFS)	Recurrence-Free Survival (RFS)
Stage I	98%	1A 1B/2A 2B	>99% 98% 91%	98% 90% 86%	98% 88% 76%
Stage II	90%	1A 1B/2A 2B	98% 91% 85%	89% 82% 60%	73% 71% 44%
Stage III	77%	1A 1B/2A 2B	94% 85% 62%	68% 68% 42%	58% 53% 33%

Greenhaw et al. JAAD 2020

Castle Biosciences, CLIA# 03D2096304 3737 N. 7th Street, Suite 160, Phoenix, AZ 85014 Tel: 866-788-9007 Fax: 866-329-2224 Version 11.0 09/01 ©2021

NEW INTEGRATED TEST RESULT WITH PRECISE AND PERSONALIZED i31-ROR AND i31-SLNB

DecisionDx-MELANOMA HCP Guide to the Patient Report

Personalized Risk Prediction Integrated with Clinicopathologic Factors

i31-SLNB for Risk of Positive Sentinel Lymph Node Assessment

- i31-GEP for SLNB now called **i31-SLNB** incorporating clinicopathologic factors with the 31-GEP continuous score to provide **precise, personalized likelihood of positive SLNB**.
- Artificial intelligence-based neural network algorithm (i31-SLNB)
- Algorithm was developed in 1,398 patients with T1-T4 cutaneous melanoma and independently validated in 1,674 consecutively tested patients.

NEW Whitman et al. i31-SLNB validation publication now available

Guidelines Suggest

- <5% likelihood: avoid SLNB
- 5-10% likelihood: discuss and consider SLNB
- >10% likelihood: recommend SLNB

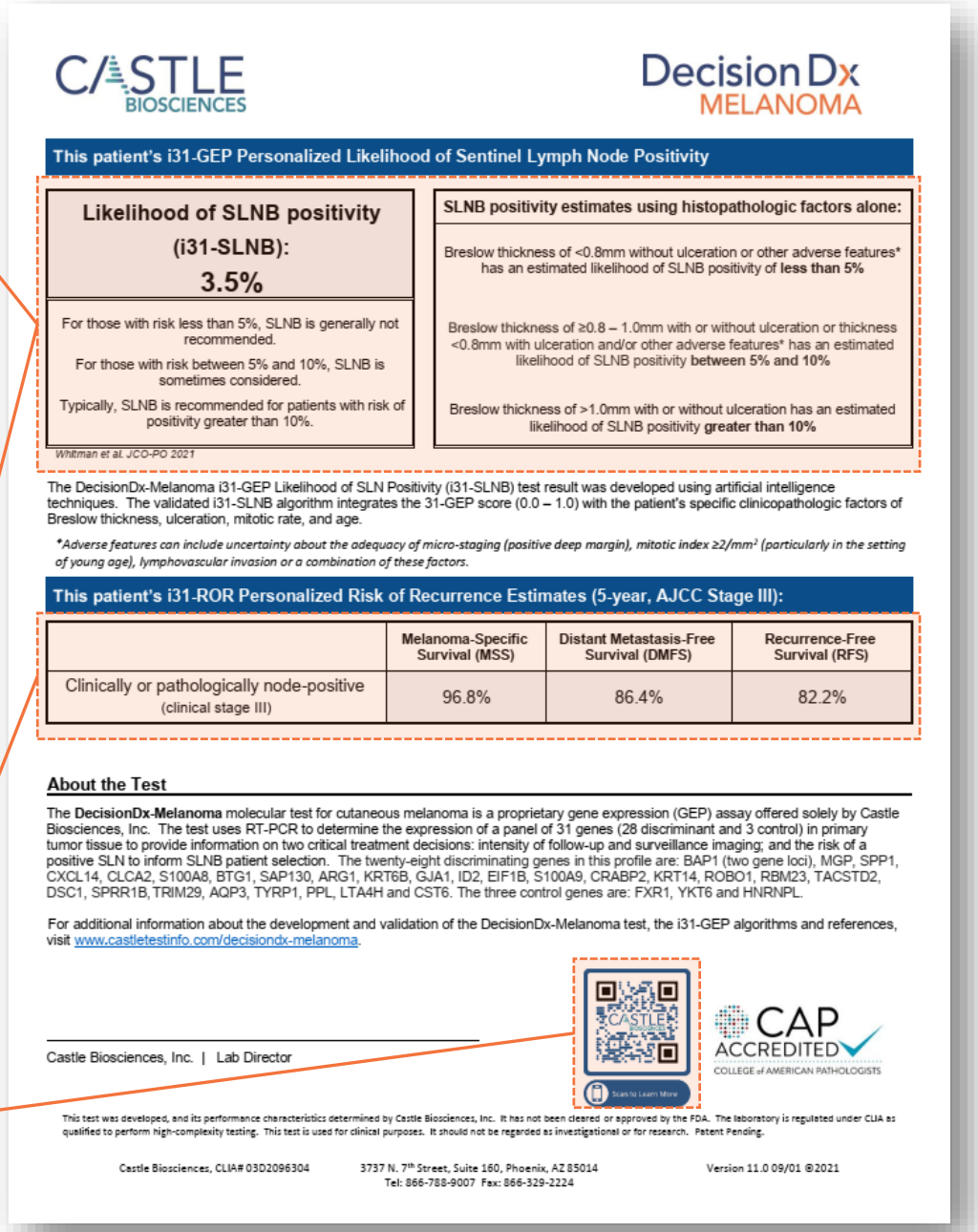
5-Year Outcomes for **Stage III Patients**

NEW i31-ROR Personalized Risk of Recurrence Estimates

- Personalized 5-year outcomes for melanoma specific survival (MSS), distant metastasis-free survival (DMFS) and recurrence-free survival (RFS) for stage III patients.

NEW QR code provides easy link to more information about DecisionDx-Melanoma at:

www.CastleTestInfo.com/DecisionDx-Melanoma



CASTLE BIOSCIENCES

DecisionDx MELANOMA

This patient's i31-GEP Personalized Likelihood of Sentinel Lymph Node Positivity

Likelihood of SLNB positivity (i31-SLNB): 3.5%	SLNB positivity estimates using histopathologic factors alone:
For those with risk less than 5%, SLNB is generally not recommended. For those with risk between 5% and 10%, SLNB is sometimes considered. Typically, SLNB is recommended for patients with risk of positivity greater than 10%.	Breslow thickness of <0.8mm without ulceration or other adverse features* has an estimated likelihood of SLNB positivity of **less than 5%** Breslow thickness of ≥0.8 – 1.0mm with or without ulceration or thickness <0.8mm with ulceration and/or other adverse features* has an estimated likelihood of SLNB positivity **between 5% and 10%** Breslow thickness of >1.0mm with or without ulceration has an estimated likelihood of SLNB positivity **greater than 10%**

Whitman et al. JCO-PO 2021

The DecisionDx-Melanoma i31-GEP Likelihood of SLN Positivity (i31-SLNB) test result was developed using artificial intelligence techniques. The validated i31-SLNB algorithm integrates the 31-GEP score (0.0 – 1.0) with the patient's specific clinicopathologic factors of Breslow thickness, ulceration, mitotic rate, and age.

**Adverse features can include uncertainty about the adequacy of micro-staging (positive deep margin), mitotic index ≥2/mm² (particularly in the setting of young age), lymphovascular invasion or a combination of these factors.*

This patient's i31-ROR Personalized Risk of Recurrence Estimates (5-year, AJCC Stage III):

	Melanoma-Specific Survival (MSS)	Distant Metastasis-Free Survival (DMFS)	Recurrence-Free Survival (RFS)
Clinically or pathologically node-positive (clinical stage III)	96.8%	86.4%	82.2%

About the Test

The **DecisionDx-Melanoma** molecular test for cutaneous melanoma is a proprietary gene expression (GEP) assay offered solely by Castle Biosciences, Inc. The test uses RT-PCR to determine the expression of a panel of 31 genes (28 discriminant and 3 control) in primary tumor tissue to provide information on two critical treatment decisions: intensity of follow-up and surveillance imaging; and the risk of a positive SLN to inform SLNB patient selection. The twenty-eight discriminating genes in this profile are: BAP1 (two gene loci), MGP, SPP1, CXCL14, CLCA2, S100A8, BTG1, SAP130, ARG1, KRT6B, GJA1, ID2, EIF1B, S100A9, CRABP2, KRT14, ROBO1, RBM23, TACSTD2, DSC1, SPRR1B, TRIM29, AQP3, TYRP1, PPL, LTA4H and CST6. The three control genes are: FXR1, YKT6 and HNRNPL.

For additional information about the development and validation of the DecisionDx-Melanoma test, the i31-GEP algorithms and references, visit www.castletestinfo.com/decisiondx-melanoma.

Castle Biosciences, Inc. | Lab Director

CAP ACCREDITED COLLEGE of AMERICAN PATHOLOGISTS

This test was developed, and its performance characteristics determined by Castle Biosciences, Inc. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Patent Pending.

Castle Biosciences, CLIA# 03D2096304 | 3737 N. 7th Street, Suite 160, Phoenix, AZ 85014 Tel: 866-788-9007 Fax: 866-329-2224 | Version 11.0 09/01 ®2021

Your Patients Have Access to an Industry-Leading Financial Assistance Program

Healthcare Provider Signs Letter of Medical Necessity (LOMN)

- A signed LOMN will be needed and can be submitted with the test requisition form
- For your convenience, a LOMN template is available upon request

Castle Biosciences Submits Claim to Patient's Insurance Company

- After a patient report is issued, Castle Biosciences bills all third party insurance including Medicare/Medicaid and VA
- Castle Biosciences will send a letter to the patient notifying them of our claim submission

Patient Receives Explanation of Benefits (EOB)

- Patients will receive an EOB from their insurance plan
- This is not a bill, but the EOB may show an "Amount Due From Patient" or state "Patient Responsibility"

Patient Asked to Sign Appeal Consent Form

- Depending on the patient's insurance plan requirements, Castle Biosciences may require assistance during the reimbursement process to file claims and appeals on the patient's behalf

At Castle Biosciences, our goal is to ensure all patients have access to our tests. We believe the availability of testing should not be limited by a patient's ability to pay.

Reimbursement Information or Questions:
866-788-9007, option 3
Reimbursement@CastleBiosciences.com
CastleTestInfo.com

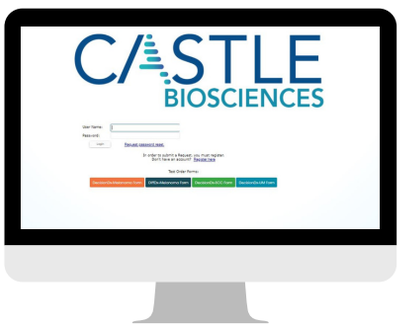
DecisionDx MELANOMA DecisionDx·SCC

Ordering a DecisionDx test for your patient is a simple process.

1. **Requisition Form (Completed & Signed)**
   - Hard Copy or Utilize Online Portal
2. **Letter of Medical Necessity (Completed & Signed)**
3. **Pathology Report(Primary Biopsy Specimen)**
   - Include Excision Report if Available
4. **Copy of Patient's Insurance Information**

Submit all documentation at
Portal.CastleBiosciences.com or fax to 866-329-2224

Convenient Physician Portal



- HIPAA compliant and secure
- Order online or download pdf order forms
- Easily access patient test information 24/7
- Upload all supporting documents including LOMN, pathology reports and patient insurance information
- Receive email notifications when a report is available to view

Results are typically available within 5 days from sample receipt.

For further information, please contact your Area Manager or call the Customer Service Team at 866-788-9007, option 1.

CASTLE BIOSCIENCES

CASTLE BIOSCIENCES

3737 N 7th Street, Suite 160
Phoenix, AZ 85014
Customer Service: 866-788-9007

Fax completed form to: 866-329-2224
Alternate fax: 602-266-9597

DecisionDx-MELANOMA
DecisionDx-CMSeq

Requisition Form

I. Ordering Entity Information

Name of Ordering Physician, PA, NP*

Specialty NPI

Address*

City / State / Zip*

( ) ( )
Telephone* Fax*

Institution / Practice Name*

II. Patient Information

Last Name* First Name* MI

DOB* Gender SSN / MR#

Address*

City / State / Zip*

( )
Telephone*

Email

III. Billing Information

Submitting Diagnosis ICD-10 Code*

Method of Payment:
- ☐ Private Insurance ☐ Patient Self-Pay
- ☐ Medicare ***Section V required*** ☐ Medicaid
- ☐ Client Bill *(contracted entities only)*

Primary Insurance Co. Name Policy#

( )
Insurance Co. Phone#

Secondary Insurance? ☐ Yes ☐ No
(If yes, attach copy of front/back of secondary insurance card)

IV. Test Menu (REQUIRED)

Primary Test: ☐ DecisionDx-Melanoma Gene Expression Profile

Additional Testing: (check box, if desired) ☐ DecisionDx-CM***Seq*** Sequencing Test *(BRAF, NRAS, KIT)*

V. Medicare Only **Required for patients with traditional Medicare as primary insurance*

At time of tissue collection, was this patient: ☐ Non-hospital ☐ Hospital Outpatient ☐ Hospital Inpatient If hospital inpatient, date of discharge: _____

If specimen is stored for more than 30 days from the date of collection, please provide the date specimen is pulled from archive: _____

VI. Clinical Information **REQUIRED FOR ALL PATIENTS*

Has the patient had a sentinel lymph node biopsy for *this* melanoma? ☐ N ☐ Y

If yes, what was the result? ☐ Neg ☐ Pos (please provide surg report)

Does/Did this patient have clinically palpable node(s)? ☐ N ☐ Y

Does/Did this patient have intransit metastasis? ☐ N ☐ Y

VII. Required Signature

X

SIGNATURE OF TREATING CLINICIAN*

Printed Name

Date

This signature confirms this test to be medically necessary for this patient. This clinician provides consultation and/or treatment for melanoma and will use the results in the management of the patient.

VIII. Additional Order Information

Name of Treating Clinician *(if different than section I)*

( ) ( )
Phone # Fax#

Mailing Address (☐ same as requestor)

City / State / Zip

Institution/Practice Name

Email address for report notification

Additional Clinician *(optional)*

( ) ( )
Phone # Fax#

Mailing Address (☐ same as requestor)

City / State / Zip

Institution/Practice Name

Email address for report notification

IX. Laboratory Information

Please fax this requisition along with a copy of the pathology report from the *primary* biopsy and excision *(if available)*

Facility where tissue is maintained: _____ Date of Collection: _____

Phone: _____ Fax: _____

FOR INTERNAL USE ONLY

Received: _____ Processed by: _____ Materials received: _____

PR/Initials: _____ DTL: _____ Note: _____

CASTLE BIOSCIENCES
3737 N 7th Street, Suite 160
Phoenix, AZ 85014
Customer Service: 866-788-9007

DecisionDx-MELANOMA
DecisionDx-CMSeq

Requisition Form Completion Instructions

1. **Section I**: Complete with information of the ordering Entity.

2. **Section II**: Complete with patient information.

3. **Section III**: Provide the ICD-10 code and patient's diagnosis. Select Method of Payment. Please complete with billing information including a copy of the front and back of the insurance card (if applicable). If the person completing this requisition is not in possession of the information necessary for completion of the billing information section, please provide the name/department and contact information of the appropriate party from whom this information can be obtained:

   Name: _____ Department: _____
   Phone: _____Fax: _____

   *If a copy of the front and back of the insurance card is provided, no further information is needed in this section of the requisition. A billing face sheet is also sufficient, in lieu of copy of card.

4. **Section IV**: Select the desired test by checking the appropriate box. One can order Gene Expression profile alone, DecisonDx CMSeq NGS panel alone, or both tests concurrently.

5. **Section V**: Applicable only for patients with Traditional Medicare as their primary insurance.

6. **Section VI**: Check the appropriate box regarding the patient's current sentinel lymph node biopsy status for this melanoma. If the patient has had a SLNB performed, please provide a copy of the surgical path report along with the completed requisition. Please provide information regarding presence of palpable node(s) and/or intransit metastasis.

7. **Section VII:** The ordering clinician must sign this section. **For purposes of ordering this test, the "ordering clinician" section can be signed only by a physician, advanced practice registered nurse (APRN) or representative Physician Assistant (PA)**

8. **Section VIII:** Complete with information for the treating clinician and/or additional clinicians. If the mailing address is the same as for the ordering clinician, check the box "same as requestor". Be sure to select the preferred method by which results should be communicated and provide an email address if you wish to receive electronic notification that the report is available.

9. **Section IX:** Complete this section with the name of the facility where the tissue from which slides for testing will be requested. Provide the name and phone # of an individual to whom a tissue request should be made.

FAX THE FOLLOWING DOCUMENTS TOLL FREE AT 1-866-329-2224
(Alternate fax: 602-222-5200)
*Order confirmation will be sent to the ordering clinician via fax within 24 hours of receipt

- ☐ Completed requisition
- ☐ Pathology report(s)
- ☐ Signed letter of medical necessity

DecisionDx MELANOMA

Patient Resource Guide

For more information visit:
MyMelanoma.com
866-788-9007
option #1

Understanding your options after cutaneous melanoma diagnosis

What is cutaneous melanoma?

Cutaneous melanoma is a form of skin cancer that develops when the skin cells that give skin its color (melanocytes) are damaged and begin to grow out of control. Damage to these skin cells is usually triggered by overexposure to ultraviolet (UV) radiation either from the sun or tanning beds. Though it is not the most common type of skin cancer, it is one of the most aggressive because of its ability to spread to other parts of the body.

If you or someone you love has been diagnosed with Stage I, II, or III melanoma, your healthcare professional may consider genomic testing to determine the risk of the cancer coming back (recurring) or spreading (metastasizing). This guide will help you understand important information about the DecisionDx-Melanoma genomic test, including the benefits of knowing your results.

What is your risk?

Traditional factors that indicate your tumor might be at higher risk of recurring include:

- How far the melanoma has invaded the skin (Breslow thickness)
- Whether the tumor is ulcerated
- How quickly the melanoma cells are multiplying (mitotic rate)
- Age

Today, due to advances in science, the DecisionDx-Melanoma test can provide additional, personalized information about your melanoma that traditional staging factors alone may miss.

CASTLE BIOSCIENCES

RISK IDENTIFIED

SkinMelanoma.com

What is the DecisionDx-Melanoma genomic test?

DecisionDx-Melanoma is a genomic test that uses a small sample of your melanoma tissue to measure the activity of 31 specific genes that can tell us how likely it is for the cancer to come back or spread within the next 5 years, and your likelihood of sentinel lymph node positivity.

What do the results mean?

The DecisionDx-Melanoma test result provides a genomic-based determination of your tumor's likelihood to metastasize (spread) within the next 5 years. These results should be interpreted along with your other risk factors and overall health.

The results will provide your individual risk class as one of the following:

CLASS 1A
Lowest risk of recurrence and/or metastasis

CLASS 1B/2A
Increased risk of recurrence and/or metastasis

CLASS 2B
Highest risk of recurrence and/or metastasis

Integrated Test Result:
Once your DecisionDx-Melanoma Class result is determined, it will be incorporated with your clinical and pathological risk factors (Breslow thickness, ulceration, mitotic rate,age, SLN status, and tumor location) to provide precise and personalized predictions for the risk of your cancer coming back and likelihood of sentinel lymph node positivity. These individualized test results can help you and your healthcare professional make decisions about your treatment, follow-up appointments, referrals and the SLNB surgical procedure. Typically SLNB should be discussed and considered when a patient's risk of positivity is greater than 10%. For those with risk between 5% and 10%, SLNB is sometimes considered. For those with risk less than 5%, SLNB is generally not recommended.

What are the benefits of using the test?

Your healthcare professional can use your test results, in combination with other tests and procedures, to plan your treatment and ongoing management.

How do I request the DecisionDx-Melanoma test?

If you wish to have the DecisionDx-Melanoma test performed, please discuss it with your healthcare professional. Only a healthcare professional can order this test.

How is the test paid for?

Castle Biosciences works with all insurance providers, including Medicare, Medicaid, commercial insurers, and the VA, to secure payment for the DecisionDx-Melanoma test. Castle will submit insurance claims on your behalf and provide you with an update on your claim processing status. The company also offers a Patient Assistance Program with the belief that quality care should not depend on financial considerations. You can get more information about insurance coverage, claims processing and financial assistance by calling 866-788-9007 and selecting option #3.

DecisionDx-Melanoma testing process is easy:

Step 1

Your healthcare professional orders the DecisionDx-Melanoma test

Step 2

Castle Biosciences works with your healthcare professional's pathology laboratory to obtain a tissue sample from your original biopsy

Step 3

Castle Biosciences analyzes your tissue sample with the DecisionDx-Melanoma genomic test

Step 4

Castle Biosciences sends your test results to your healthcare professional, so that they can discuss your individual results with you and determine next steps

Additional Testing Available from Castle Biosciences

DecisionDx-CMSeq

DecisionDx-CM *Seq* gene sequencing test is a separate test that can determine whether there are alterations in three important genes in your melanoma tumor, BRAF, NRAS and KIT. In certain situations, this information can help your healthcare professional determine treatment plans and may be helpful for future therapy decisions as research and treatments evolve.

DecisionDx-CM *Seq* provides different information than the DecisionDx-Melanoma test, and is NOT a substitute for the DecisionDx-Melanoma test. Talk to your healthcare provider to learn more about DecisionDx-CM *Seq* for your individual situation.

CASTLE BIOSCIENCES

Laboratory Address:
3737 N. 7th Street, Ste. 160
Phoenix, AZ 85014

CLIA-certified,
CAP-accredited laboratory

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

DDXCM-002v3-102021

CASTLE BIOSCIENCES

Insurance and Financial Information

- Your healthcare professional has ordered a DecisionDx test from Castle Biosciences to learn more about the biology of your tumor.
- The test result will help your healthcare professional decide how to best manage your care.

For questions about insurance coverage, claims processing and financial assistance call 866-788-9007, option 3 or email: Reimbursement@CastleBiosciences.com

What you can expect:

1. Castle Biosciences will submit a claim to your insurance company for the test. You will receive a letter from Castle Biosciences notifying you that your claim was submitted.

2. Your insurance company will send you an "Explanation of Benefits" (EOB). **This is not a bill.**

3. Castle Biosciences may need your consent to submit appeals on your behalf. **Please sign and return the consent form if you receive one.**

DecisionDx-Melanoma
DecisionDx-SCC
myPath Melanoma DiffDx-Melanoma

CB-0005v2-052021